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September 14, 2000

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20852

Attention: Janet Woodcock, M.D.

Re: Citizen Petition URSO/ACTIGALL
Docket No. 99 P-1659 (CP1)

Dear Dr. Woodcock:

On May 26, 1999, we submitted on behalf of Novartis Pharmaceutical Corporation, a Citizen Petition requesting that the Secretary of Food and Drugs withdraw approval for the pharmaceutical formulation URSO, which is the proprietary name being used by Axcan Pharma U.S., Inc. for ursodeoxycholic acid (ursodiol), indicated for the treatment of primary billiary cirrhosis in humans, unless the name of the product is changed.

Although we received an interim response dated December 17, 1999, indicating that a decision on the petition was pending, to date we have not received a decision from the FDA. We note that confusion among ursodiol users continues to occur due to the common use of the term "urso" for both the ACTIGALL® brand of ursodiol and the URSO® brand of ursodiol. A print out from a webpage for people affected with primary billiary cirrhosis is attached hereto. The webpage is a forum containing educational and supportive information for people with primary billiary cirrhosis.

99P165 9

LET 2

Since it has now been over a year since the Citizen Petition was filed, and more than six months since we received the interim response, we respectfully request that you inform us of when we might expect to receive a substantive response to the Citizen Petition.

Respectfully submitted,

Keith E. Sharkin

63/93/cr
Encl.

Primary Biliary Cirrhosis

United Through Education, Research & Support

PBCers Organization

Urso and PBC

The Actigall/URSO 250 discussion is confusing to many of our members. Possibly what could be confusing is the understanding Actigall and URSO 250 tablets are brand names. Also many of the doctors and pharmacies use the same name for both....Urso, and this adds to the confusion.

Chemically both Actigall & URSO 250 are made from ursodiol/ursodeoxycholic acid, but they are NOT the same product. Each has a different FDA approved indication.

Actigall (Ursodiol) 300 mg Capsules made by Novartis is indicated for patients with radiolucent, noncalcified gallbladder stones. Over the years it showed to help in PBC and is prescribed by many doctors as PBC treatment.

URSO 250 tablets made by Anxcan Scandipharm is the ONLY ursodiol product specifically for Primary Biliary Cirrhosis, as it has has the FDA approved PBC indication and extensive research testing was done. See URSO/Actigall dosage chart by weight and cost.

Ursodiol by Amide Pharm is the "generic" for Actigall.....NOT URSO 250 tablets.

Form: Memo

Dear PBCers,

Although Actigall has been used for several years by many physicians for PBC you now have an alternative. URSO®(ursodiol tablets) are the only brand of ursodiol proven to have a positive effect in patients with PBC. URSO is the brand that recently won FDA approval after more than 7 years of studies.

It is unfortunate that there remains so much confusion about URSO and PBC. However, we will attempt to shine some light on the product for you so that you may use the information to your best advantage and pass it along if you choose.

URSO and Actigall are not the same. Chemically the products are both made from ursodiol or ursodeoxycholic acid. However, that is where the similarities end. URSO is proven effective in PBC. URSO is backed by the URSOurce program, the only complete ursodiol treatment program. URSOurce is a program designed to help patients, physicians, and payers understand Cholestatic Liver Diseases such as PBC and ursodiol therapy. URSO in the US is brought to you and your physicians through the joint venture Axcan Schwarz LLC, one of the principal sponsors of "Primary Biliary Cirrhosis Conference, From Pathogenesis to Treatment", held in Chicago-November 1997.In 1998 Axcan Schwarz and URSO have sponsored over 400 physician based educational symposia on liver disease in varying areas of the country. 1) URSO is the only ursodiol product for Primary Biliary Cirrhosis. URSO dosed at 13-15 mg/kg in 4 divided doses throughout the day was proven to have beneficial effects on PBC patients in a hallmark Mayo Clinic study. This dosage is the only proven dosage to affect PBC and anecdotally it has been said to minimize potential side effects. Many PBC patients have been treated with Actigall and they have been improperly started at 10-12 mg/kg.This error commonly occurs because the dosing for Actigall is based on its only approved use, the dissolution of gallstones. US Physicians were originally introduced to ursodiol at this dosing schedule and have not had a visit from the Schwarz Pharma Sales Representative to properly instruct them on how to dose URSO for PBC. However, in the near future almost all gastroenterologists should be contacted and have sample bottles of URSO worth over $20 for you and other patients to begin therapy. 2) URSO is the brand name of a 250mg ursodiol tablet tested and specifically proven to increase the time to Liver transplant and decrease the incidence of esophageal varices in PBC patients. URSO is not the first ursodiol product to market in the USA. Actigall has been on pharmacists shelves for almost 10 years. Some pharmacists are improperly making the assumption that both ursodiol products are the same. However, the US Food and Drug Administration denied an application for Actigall's effectiveness in PBC. For your information the Pharmacists who are dispensing Actigall when the physician prescribes URSO, are essentially breaking the law if they do not get clearance from you and your physician to make the substitution. URSO is a white tablet with "UR785" imprinted on it. Actigall is a pink and white capsule with Actigall 300mg imprinted on it.

3) Through the different distribution channels (wholesaler, retailer, hospital), URSO should always cost less than Actigall, even though URSO isa 250mg tablet and Actigall is a 300mg capsule. We have priced URSO when itleaves our shipping dock to be 10% less than Actigall on a mg per mg basis.In other words for 1 mg of URSO it costs 10% less than 1 mg of Actigall. Also, we have set up a Reimbursement Advocate who can help any URSO patientgain reimbursement for the expense of the product (1-888-877-6471). If a patient can not afford the cost of URSO therapy and does not have insurancecoverage, we have joined forces with the American Liver Foundation to offeran URSO Patient Assistance Program(PAP). The URSO PAP will help indigent patients by supplying free therapy for a full year.

PBCers, we appreciate your comments and questions and hope this information helps you decide on the proper course for your website. Please let us know if we can be of any other assistance.

Sincerely,

Stephen M. Casey

Director of Management

Axcan Schwarz LLC

Use Proportional Font: true

Previous From: SCASEY @ SCHWUSA (Steve Casey)

Attachment Count: 1

Attachment Date: 9/28/98 3:15 PM,12/12/97 11:40 AM

URSO®

Ursodiol Tablets 250 mg

DESCRIPTION

URSO® is a bile acid available as 250 mg film-coated tablets for oral administration.

URSO® is ursodiol (ursodeoxycholic acid), a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting white powder consisting of crystalline particles freely soluble in ethanol and glacial acetic acid, slightly soluble in chloroform, sparingly soluble in ether, and practically insoluble in water. The chemical name of ursodiol is 324H40O4). Ursodiol has a molecular weight of 392.56. Its structure is shown below.

Inactive ingredients: microcrystalline cellulose, povidone, sodium starch glycolate, magnesium stearate, ethylcellulose, dibutyl sebacate, carnauba wax, hydroxypropyl methylcellulose, PEG 3350, PEG 8000, cetyl alcohol, sodium lauryl sulfate, and hydrogen peroxide.

CLINICAL PHARMACOLOGY

Ursodiol (UDCA) is normally present as a minor fraction of the total bile acids in humans (about 5%). Following oral administration, the majority of ursodiol is absorbed by passive diffusion and its absorption is incomplete. Once absorbed, ursodiol undergoes hepatic extraction to the extent of about 50% in the absence of liver disease. As the severity of liver disease increases, the extent of extraction decreases. In the liver, ursodiol is conjugated with glycine or taurine, then secreted into bile. These conjugates of ursodiol are absorbed in the small intestine by passive and active mechanisms. The conjugates can also be deconjugated in the ileum by intestinal enzymes, leading to the formation of free ursodiol that can be reabsorbed and reconjugated in the liver. Nonabsorbed ursodiol passes into the colon where it is mostly 7-dehydroxylated to lithocholic acid. Some ursodiol is epimerized to chenodiol (CDCA) via a 7-oxo intermediate. Chenodiol also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic acid is reabsorbed, conjugated in the liver with glycine, or taurine and sulfated at the 3 position. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in feces.

Lithocholic acid, when administered chronically to animals, causes cholestatic liver injury that may lead to death from liver failure in certain species unable to form sulfate conjugates. Ursodiol is 7-

dehydroxylated more slowly than chenodiol. For equimolar doses of ursodiol and chenodiol, steady state levels of lithocholic acid in biliary bile acids are lower during ursodiol administration than with chenodiol administration. Humans and chimpanzees can sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals. Nonetheless, such a deficiency has not yet been clearly demonstrated and must be extremely rare, given the several thousand patient-years of clinical experience with ursodiol.

In healthy subjects, at least 70% of ursodiol (unconjugated) is bound to plasma protein. No information is available on the binding of conjugated ursodiol to plasma protein in healthy subjects or primary biliary cirrhosis (PBC) patients. Its volume of distribution has not been determined, but is expected to be small since the drug is mostly distributed in the bile and small intestine. Ursodiol is excreted primarily in the feces. With treatment, urinary excretion increases, but remains less than 1% except in severe cholestatic liver disease.

During chronic administration of ursodiol, it becomes a major biliary and plasma bile acid. At a chronic dose of 13-15 mg/kg/day, ursodiol constitutes 30-50% of biliary and plasma bile acids.

CLINICAL STUDIES

A U.S., multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of ursodeoxycholic acid at a dose of 13-15 mg/kg/day, administered in 4 divided doses in 180 patients with PBC. Upon completion of the double-blind portion, all patients entered an open-label active treatment extension phase.

Treatment failure, the main efficacy end point measured during this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal. After two years of double-blind treatment, the incidence of treatment failure was significantly reduced in the URSO® group (n=89) as compared to the placebo group (n=91).

Time to treatment failure was also significantly delayed in the URSO® treated group regardless of either histologic stage or baseline bilirubin levels (>1.8 or . Using a definition of treatment failure which excluded doubling of serum bilirubin and voluntary withdrawal, time to treatment failure was significantly delayed in the URSO® group. In comparison with placebo, treatment with URSO® resulted in a significant improvement in the following serum hepatic biochemistries when compared to baseline: total bilirubin, SGOT, alkaline phosphatase and IgM.

A second study conducted in Canada randomized 222 PBC patients to ursodiol, 14 mg/kg/day or placebo, in a double-blind manner during a two-year period. At two years, a statistically significant difference between the two treatments, in favor of ursodiol, was demonstrated in the following: reduction in the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent decrease in bilirubin, transaminases and alkaline phosphatase; incidence of treatment failure; and time to treatment failure. The definition of treatment failure included: discontinuing the study for any reason; a total serum bilirubin level greater than or equal to 1.5 mg/dl or increasing to a level equal to or greater than two times the baseline level; and the development of ascites or encephalopathy.

INDICATIONS AND USAGE

URSO® (ursodiol) tablets are indicated for the treatment of patients with primary biliary cirrhosis.

CONTRAINDICATIONS

Hypersensitivity or intolerance to ursodiol or any of the components of the formulation.

PRECAUTIONS

Patients with variceal bleeding, hepatic encephalopathy, ascites or in need of an urgent liver transplant, should receive appropriate specific treatment.

Drug Interactions

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of URSO® by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with URSO® in the same manner as the bile acid sequestering agents. Estrogens, oral contraceptives, and clofibrate (and perhaps other lipid-lowering drugs) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of URSO®.

Carcinogenicity, Mutagenicity and Impairment of Fertility

In two 24-month oral carcinogenicity studies in mice, ursodiol at doses up to 1,000 mg/kg/day (3,000 mg/m2/day) was not tumorigenic. Based on body surface area, for a 50 kg person of average height (1.46 m2 body surface area), this dose represents 5.4 times the recommended maximum clinical dose of 15 mg/kg/day (555 mg/m2/day).

In a two-year oral carcinogenicity study in Fischer 344 rats, ursodiol at doses up to 300 mg/kg/day (1,800 mg/m2/day, 3.2 times the recommended maximum human dose based on body surface area) was not tumorigenic.

In a life-span (126-138 weeks) oral carcinogenicity study, Sprague-Dawley rats were treated with doses of 33 to 300 mg/kg/day, 0.4 to 3.2 times the recommended maximum human dose based on body surface area. Ursodiol produced a significantly (p's exact test) increased incidence of pheochromocytomas of the adrenal medulla in females of the highest dose group.

In 103-week oral carcinogenicity studies of lithocholic acid, a metabolite of ursodiol, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumors. In a 78-week rat study, intrarectal instillation of lithocholic acid (1 mg/kg/day) for 13 months did not produce colorectal tumors. A tumor-promoting effect was observed when it was administered after a single intrarectal dose of a known carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. On the other hand, in a 32-week rat study, ursodiol at a daily dose of 240 mg/kg (1,440 mg/m2, 2.6 times the maximum recommended human dose based on body surface area) suppressed the colonic carcinogenic effect of another known carcinogen azoxymethane.

Ursodiol was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, TK+/-) forward mutation test, the human lymphocyte sister chromatid exchange test, the mouse spermatogonia chromosome aberration test, the Chinese hamster micronucleus test and the Chinese hamster bone marrow cell chromosome aberration test.

Ursodiol at oral doses of up to 2,700 mg/kg/day (16,200 mg/m2/day, 29 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and

reproductive performance of male and female rats.

Pregnancy, Teratogenic Effects. Pregnancy Category B

Teratology studies have been performed in pregnant rats at oral doses up to 2,000 mg/kg/day (12,000 mg/m2/day, 22 times the recommended maximum human dose based on body surface area) and in pregnant rabbits at oral doses up to 300 mg/kg/day (3,600 mg/m2/day, 7 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to ursodiol.

There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether ursodiol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when URSO® is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of URSO® in pediatric patients have not been established.

ADVERSE EVENTS (AEs)

ADVERSE EVENTS VISIT AT 12 MONTHS VISIT AT 24 MONTHS

UDCA n (%) Placebo n (%) UDCA n (%) Placebo n (%)

Diarrhea --- --- 1 (1.32) ---

Elevated creatinine --- --- 1 (1.32) ---

Elevated blood glucose 1 (1.18) --- 1 (1.32) ---

Leukopenia --- --- 2 (2.63) ---

Peptic ulcer --- --- 1 (1.32) ---

Skin rash --- --- 2 (2.63) ---

Note: Those AEs occurring at the same or higher incidence in the placebo as in the UDCA group have been deleted from this table (this includes diarrhea and thrombocytopenia at 12 months, nausea/vomiting, fever and other toxicity).

UDCA=Ursodeoxycholic acid=Ursodiol

Adverse events are reported regardless of attribution to the test medication.

OVERDOSE

Accidental or intentional overdosage with ursodiol has not been reported. The most severe manifestation of overdosage would likely consist of diarrhea which should be treated symptomatically.

Single oral doses of ursodiol at 10, 5 and 10 g/kg in mice, rats and dogs, respectively were not lethal. A single oral dose of ursodiol at 1.5 g/kg was lethal in hamsters. Symptoms of acute toxicity were salivation and vomiting in dogs, and ataxia, dyspnea, ptosis, agonal convulsions and coma in hamsters.

DOSAGE AND ADMINISTRATION

The recommended adult dosage for URSO® in the treatment of PBC is 13-15 mg/kg/day administered in four divided doses with food.

HOW SUPPLIED

Each URSO® film-coated tablet, white, imprinted with "785", contains 250 mg of ursodiol. Available in bottles of 100 tablets (NDC 0091-0785-01). Store at 20 °C to 25 °C (68 °F to 77 °F). Dispense in a tight container.

Caution: Federal law prohibits dispensing without a prescription.

Manufactured by:

SCHERING CANADA INC.

Pointe-Claire, QC H9R 1B4

Canada

for:

AXCAN PHARMA U.S. INC.

3940 Quebec Avenue North

Minneapolis, MN 55427

USA

Distributed by:

SCHWARZ PHARMA

Milwaukee, WI 53201

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TO: Dockets Management Branch
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Department of Health and Human Services
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